

CHANGES IN TISSUE SENSITIVITY ASSOCIATED WITH
VARYING LIFE SITUATIONS AND EMOTIONS;
THEIR RELEVANCE TO ALLERGY*†

DAVID T. GRAHAM, STEWART WOLF, AND HAROLD G. WOLFF, NEW YORK, N. Y.

IT IS the purpose of this paper to present further evidence on three points: (1) that man reacts adaptively or protectively in similar ways to a variety of noxious stimuli; (2) that he may react to threats or symbols of assault as though they were assaults; and (3) that consequently it may be difficult to ascertain what aspects of a total situation are really relevant to the observed reactions of the individual. In particular, ingested chemical agents and foods may sometimes take on special significance not dependent on their chemical or physical structure.

The study of cutaneous vascular reactions in patients with urticaria, reported in detail elsewhere,¹ is illustrative. Thirty subjects, 17 women and 13 men, who had had repeated attacks of hives or whose present attack had lasted for 3 weeks or longer, were studied. In each case a relatively complete life history was obtained, with particular reference to an understanding of the setting in which the first and subsequent attacks occurred. An important part of such understanding was a knowledge of the patient's feelings about the situation and his general behavior with respect to it. Note was made of foods ingested and of exposure to other substances which might conceivably have acted as allergens. It was found that there was an almost invariable relationship between an attitude of a particular kind and attacks of urticaria. The patients considered themselves wronged or injured and felt that they could do nothing to improve the situation. No correlation between exposure to allergens and attacks of the disease was discovered.

In an experimental setting, and following suitable control observations, significant events known to have been associated in the past with outbreaks of hives were brought up for discussion and dwelt on for several minutes. The experiment concluded with a period of strong reassurance and diversion. During the entire experiment measurements of cutaneous vascular reactions were carried out.

All of the patients were seen to flush when topics of significant personal concern evoking resentment were discussed. Measurement revealed that at such times there was decrease in tonus of the minute vessels (capillaries and venules) and dilatation of arterioles. In 5 cases, urticarial lesions appeared during stressful interviews. Fig. 1 illustrates a typical experiment.

Lewis² pointed out that dilatation of minute vessels and of arterioles, respectively, was responsible for the first two elements of the "triple response," the red reaction and the flare. The third factor, increased vascular permeability

*From The New York Hospital and the Departments of Medicine (Neurology) and Psychiatry, Cornell University Medical College, New York, N. Y.

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which leads to whealing, is probably simply the result of the first two.¹ He showed that the complete response was evoked by many different kinds of trauma to the skin. Erythema and whealing are, in other words, part of the response of the organism to a variety of different assaults.

The results of the experiments carried out using the patients as subjects show that exactly the same cutaneous vascular reactions may occur in response to the symbolically traumatic situations of daily life. It was, furthermore, possible to show in a healthy man that the loss of minute vessel tone which follows a blow will also take place if a blow is merely threatened (Fig. 2).

The increased readiness for vasodilatation in the skins of the patients as opposed to those of individuals without skin disease was also manifested in dermographism. Striking, moreover, was the occurrence of whealing when histamine and pilocarpine were applied by iontophoresis in concentrations lower than those which evoked responses in control subjects.

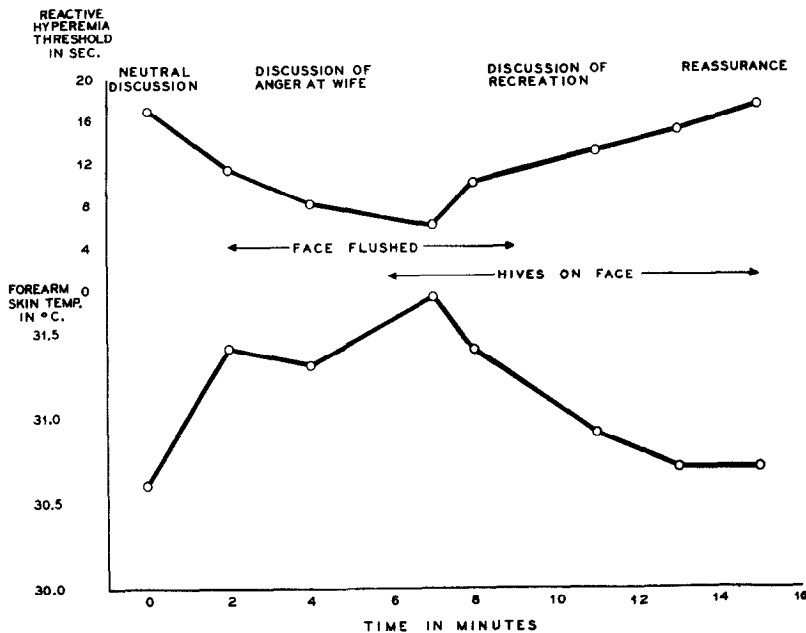


Fig. 1.—Experimental interview during which the patient developed hives. Decrease in reactive hyperemia threshold indicates loss of tone (i.e., increased tendency to dilatation) in minute vessels (venules and capillaries); rise in skin temperature indicates dilatation of arterioles. Dilatation of both sets of vessels associated with resentment culminated in the development of urticarial lesions which required some time to disappear despite reversal of the vascular changes.

In 1 patient it was possible to alter the response of the skin to histamine and pilocarpine from negative to positive, and then to reverse it again, by introduction of suitable topics for discussion (Fig. 3). In another, the same changes were demonstrated using histamine alone.

Results of study of an analogous type of allergic reaction involving the nasal mucous membrane have been presented by Holmes, Goodell, Wolf, and Wolff.³ Nasal secretions of the subjects were collected and stained by an appropriately standardized technique before, during, and after the discussion of

significant conflicts. At the same time white blood cell counts were made on the peripheral blood. It was found that nasal hyperfunction in association with stress was accompanied by a marked eosinophilia locally and in the peripheral blood as well. The reaction is illustrated in Fig. 4. In this subject, as well as in others, not only was an eosinophilic reaction observed in company with stress, but there was also a purulent response with the outpouring by the nasal membranes of polymorphonuclear leucocytes.

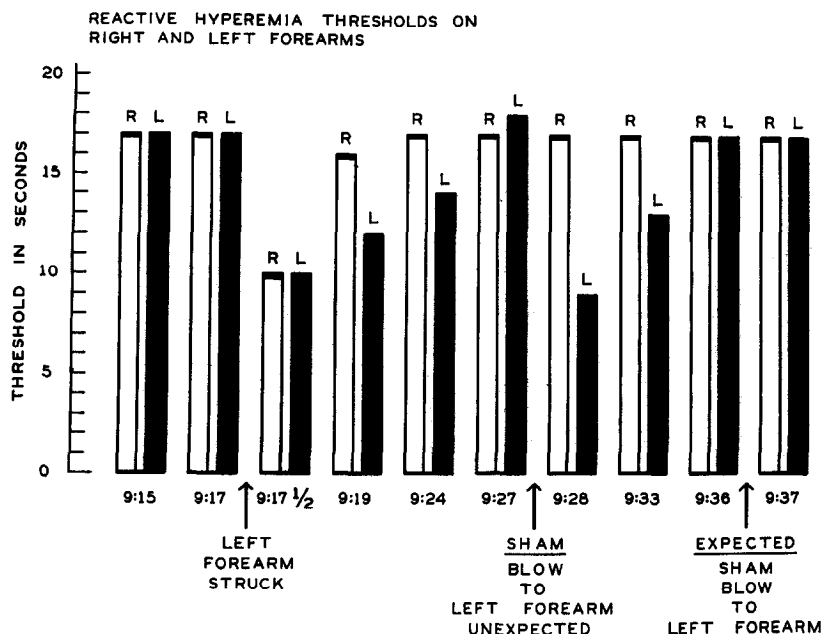


Fig. 2.—Loss of tone in minute vessels in skin of a healthy man occurring in response to a blow and to the mere threat of a blow.

Food Sensitivity

It is conceivable that foods, by virtue of particular chemical or physical structure, sometimes give rise to antigen-antibody reactions and subsequent clinical manifestations of food sensitivity. The evidence for and against the occurrence of such reactions and their importance in clinical medicine is difficult to evaluate. In any event, however, before it may be inferred that such reactions do exist and are clinically important, patients suspected of food sensitivities must be tested so as to preclude conditioning factors, since all the reactions may be exhibited in response to stimuli which have a threatening or other significance to the particular individual concerned.

It has been maintained that migraine headache is frequently a manifestation of food "allergy." The difficulties involved in reaching such a conclusion are illustrated by the following experiment.⁴

Four able physicians, experienced in experimental methods, and themselves migraine patients, were the subjects. These 4 physicians, who were of the opinion that they could predictably produce migraine headache in themselves

by eating chocolate in any form and in minimal amounts, were each given a set of lettered, sealed envelopes, with the key to the contents held in the laboratory and unknown to the subject. Each envelope contained either 8 Gm. powdered chocolate or 8 Gm. lactose in 8 black capsules. The 2 sets of capsules were indistinguishable in appearance. Two subjects ingested the contents of an envelope at convenient intervals. One subject ingested the contents at regular intervals, 3 times a week. The fourth subject, who commonly awoke on Saturday morning with a migraine headache attack after eating chocolate on Friday evening, ingested his capsules on Friday evenings for a period of 4 months. All were instructed to include no chocolate in their regular diet. Careful records were kept by each subject, including the following data: the letter on the envelope, the date and time of ingestion of the contents, the date and time of onset of all headaches experienced during the experimental period.

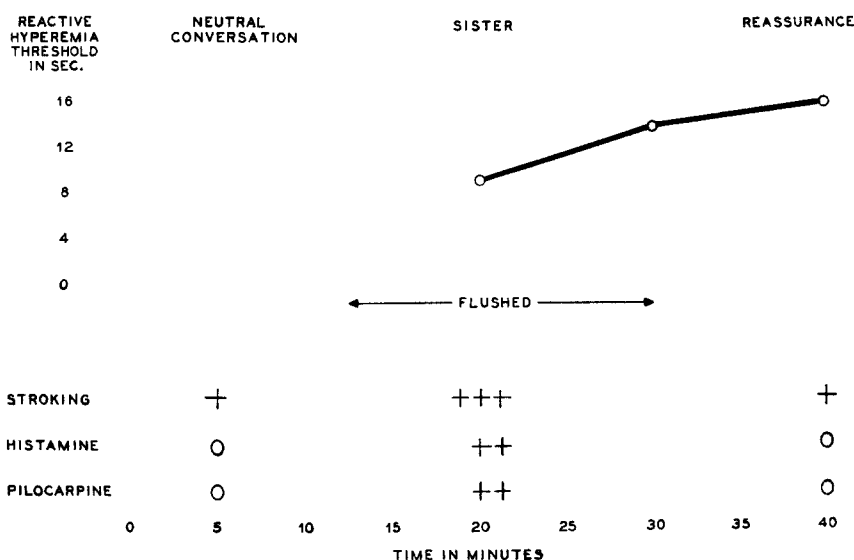


Fig. 3.—Simultaneous changes in the response of the skin to histamine, to pilocarpine, and to stroking during a stressful interview with a woman patient with hives (histamine acid phosphate 0.001 per cent and pilocarpine hydrochloride 1 per cent at 10 microamperes for 2 minutes over 1 square centimeter). There was no response to isotonic sodium chloride solution applied in the same way before, during, or after the period of stress.

It was found in these subjects that headaches sometimes followed the chocolate, sometimes the lactose, but most commonly attacks occurred without reference to the ingestion of capsules. Migraine headaches followed the ingestion of lactose just as frequently as they followed the ingestion of chocolate. The data thus accumulated indicate that, in these individuals who considered themselves "allergic" to chocolate even in minimal amounts, the occurrence of their headaches was no more related to the ingestion of chocolate than it was to the ingestion of lactose.

No well-controlled clinical study has yet been reported to support the contention that migraine headache is an allergic reaction, or to prove that the benefit from prescribed diets is specifically due to elimination of offending

allergens. It is conceivable, as mentioned above, that food sensitivity of an allergic nature does occasionally induce a headache such as has been discussed in connection with the nose. It is pointed out that the mucous membranes of the nasal and paranasal structures exhibit vasomotor changes as a part of the reaction to allergens and may give rise to headache. But in the case of the headache which accompanies the nose reaction, as well as in the case of the migraine headaches, the assumption that the allergens are responsible for the symptom must be closely questioned in any given case until proved valid.

The following observations further emphasize the necessity for caution. They were made on patients in whom food sensitivities seemed relevant to their major complaints. The patients were able to relate closely their symptoms to the ingestion of even minimal amounts of the supposedly noxious substance. A simple experiment demonstrated how unpredictable the relationship was, the reaction being apparently more dependent on seeing, tasting, smelling, and hearing of the agent than upon its chemical and physical nature.

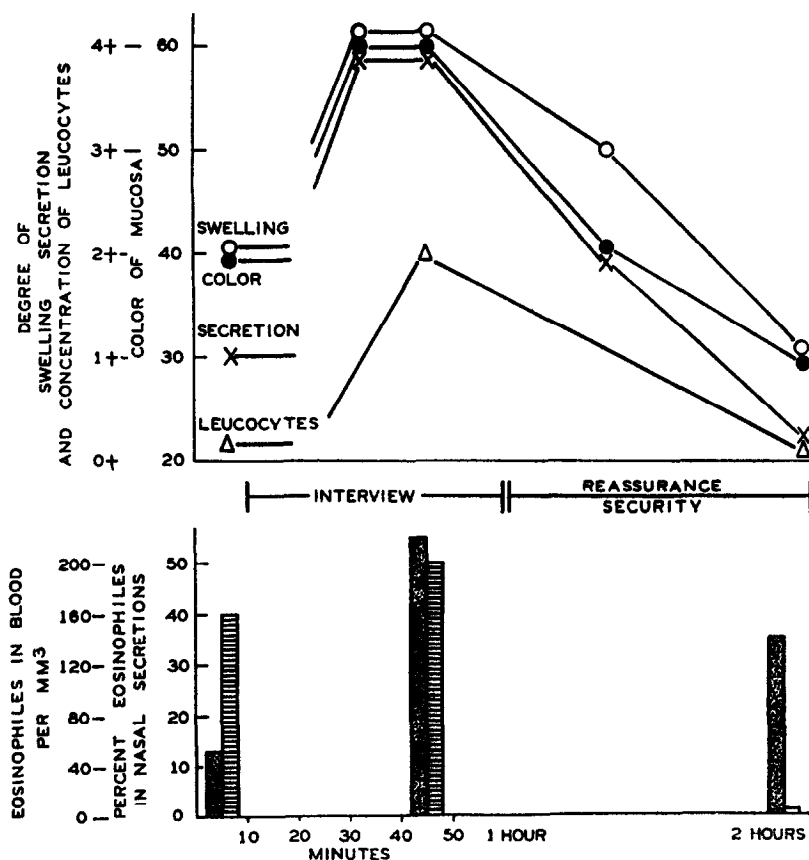


Fig. 4.—Changes in nasal mucous membrane and eosinophiles in peripheral blood during stressful interview.

CASE REPORTS

CASE 1.—A 50-year-old woman, whose chief complaints were “pressure” in her head, “poor thinking and memory,” “vision not clear,” “dizziness,” abdominal cramps, nausea,

hives, and abdominal "bloating," was studied. The symptoms occurred within 10 to 20 minutes after ingesting milk or milk products. It was stated that 4 drops of milk in a glass of water produced attacks of the above nature. She had had these attacks for 11 years, beginning after a Caesarean section. The patient had "never liked milk" but had taken a great deal of it during this pregnancy, during which she gained 60 pounds. Soon after she was given a reducing diet, milk elicited the symptoms. Skin tests were positive to milk, tomatoes, peaches, peas, pork, and lobster, but symptoms were associated only with the ingestion of milk. The patient's last ingestions of milk had been 4 days and 8 days prior to the skin test.

On the occasion of the experiment, balloons were introduced into the stomach and duodenum. After a preliminary control period had established the approximate rate and amplitude of contractions (Fig. 5), 50 c.c. of whole milk were introduced into the fundus by stomach tube without the patient being able to observe what was being administered. She was told that she was being given water as a preliminary testing procedure. There was no significant change in the duodenal motility pattern and the patient exhibited no symptoms. About 2 weeks later the experiment was repeated. This time the patient was given 50 c.c. of tap water and she was told that milk was being introduced. As will be seen further from the diagram, she developed nausea and abdominal discomfort following this suggestion, associated with some change in the duodenal motility pattern.

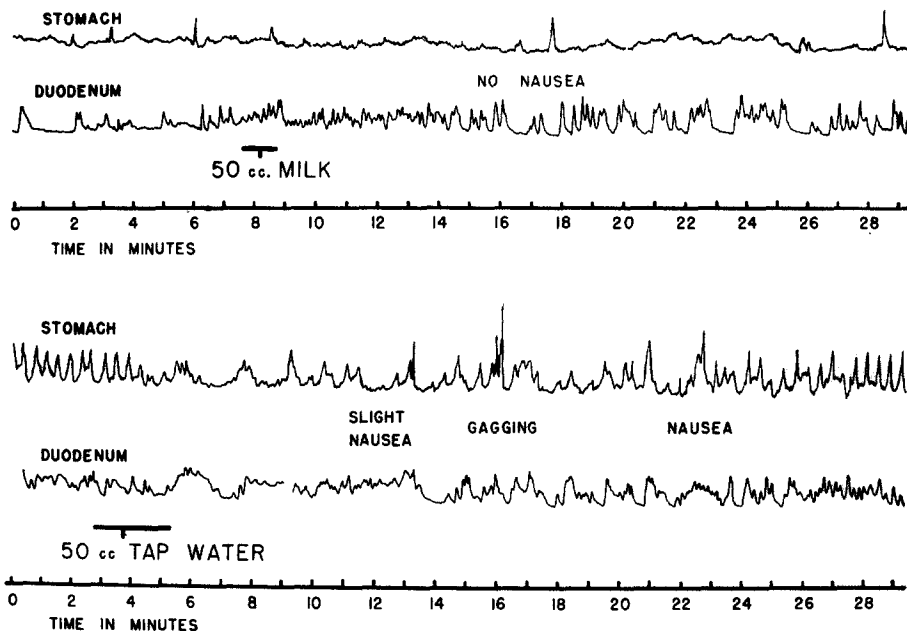


Fig. 5.—Changes in symptoms and in gastric and duodenal activity in the patient of Case 1 after the administration of milk and of tap water (see text).

CASE 2.—A 45-year-old woman, who for 28 years had had attacks of asthma within a few minutes after eating food prepared with cottonseed products, such as doughnuts, was studied. She also exhibited wheezing and dyspnea in rooms containing cotton-filled furniture. In addition she complained of abdominal cramps and nausea after eating mushrooms. Her skin and conjunctiva were sensitive to cottonseed extract. With the knowledge that she was being tested, this patient was given 1 c.c. of 100 units of cottonseed extract by mouth with no untoward results. She was then given 1 c.c. of 1,000 units of cottonseed extract by mouth which produced nausea in 9 minutes, lasting for 12 minutes. Three days later the administration of 10,000 units of cottonseed extract by mouth resulted in itchy nose and a severe asthmatic attack which persisted for 36 hours. No attempt was made to conceal from her that cottonseed was being given.

At a later date 5,000 units of cottonseed extract were given by stomach tube, the patient being told that it was water being used to test stomach motility. No symptoms ensued. Fifty minutes later, 50 c.c. of water was given and the patient was informed that she was receiving mushrooms. Nausea, abdominal pain, and bowel urgency occurred 30 minutes after the latter administration. These symptoms lasted for 20 minutes and did not recur (Fig. 6).

CASE 3.—A study was made of a 39-year-old woman who for about 3 months complained of wheezing, running eyes and nose, and hives soon after the ingestion of milk. Skin tests were positive to milk and fish. A stomach balloon was inserted and, after a control period during which motility of the stomach was observed, 50 c.c. of milk were introduced. The patient was told that the introduced liquid was water. She was then told that a specimen of gastric secretion was to be taken but actually nothing was withdrawn. Her nasal mucous membrane was examined before and after the administration of milk and it was found that there was less secretion and congestion after the milk than before. She had no wheezing (Fig. 7).

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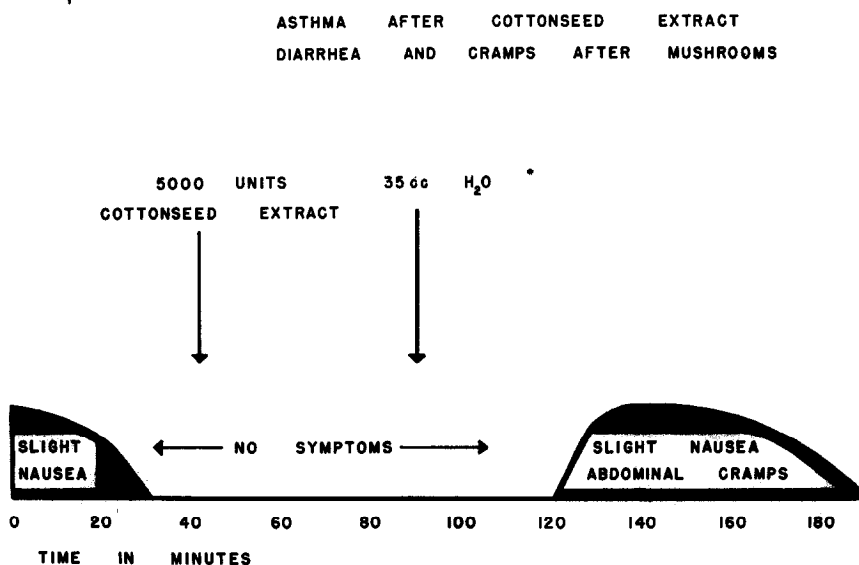


Fig. 6.—Changes in symptoms of patient of Case 2 after administration of cottonseed extract and of water (see text).

COMMENT

The inference from such demonstrations is that the relation between an ingested agent and tissue reaction may be intimate and dramatic. However, unless the circumstances of administration of the agent preclude all opportunity for conditioning factors to operate, it may not be inferred that such reactions are allergic in nature.

Thus from a series of controlled experimental studies it is inferred that arterioles and minute vessels of the skin exhibit dramatic changes in function during experimentally induced alterations in feeling states. Certain persons, during periods of resentment in reaction to symbols of assault, exhibit dilatation of arterioles and minute vessels. This constellation leads to a transudation of

fluid with resultant edema of the skin. When this is especially striking locally, it becomes tumescent edema or hives and constitutes under certain circumstances a "positive" skin test. Although such tissue alterations occur without additional mechanical stimuli from without, slight mechanical trauma, such as arises from the pressure of clothing or gentle blows, augments locally the edema in the skin. A great variety of nonspecific agents may become factors in the outward show of dermatoses when the skin is already in such a state of increased sensitivity. Moreover, the skin changes in its sensitivity to chemical agents so that amounts of histamine which under one set of life circumstances and emotions produce no reaction may, under others, evoke urticarial reactions. Indeed, during periods of stress, skin and mucous membranes may exhibit an increased sensitivity to a host of foods, pollens, drugs, and simpler chemical agents. Such increased sensitivity is not present during periods of relative tranquillity.

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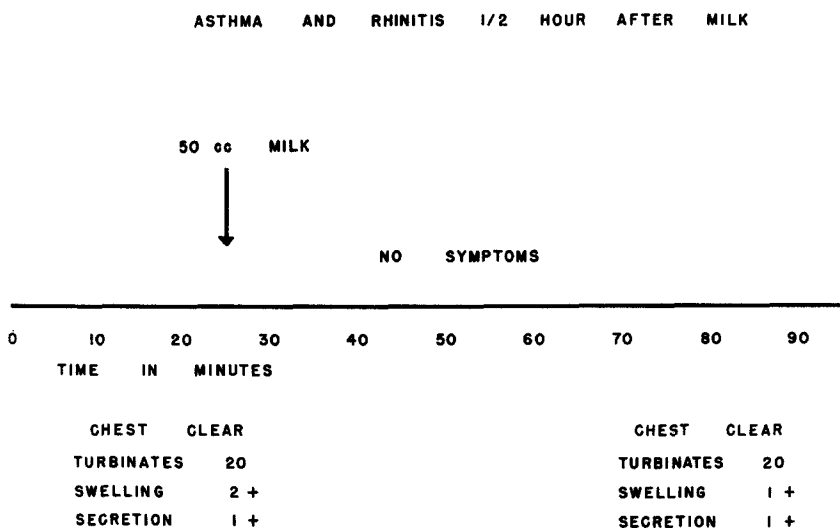


Fig. 7.—Slight decrease in edema of nasal mucosa, without change in secretion or in color of turbinates, after administration of milk. No symptoms developed. (See text, Case 3.)

It has also been shown that foods ingested under one set of conditions are followed by violent reactions which are absent when the same substances are ingested under other conditions. Therefore, in assaying the tissue sensitivity of an individual to certain assaults, including ingestion of foods, it becomes necessary to appraise their effects in terms of the setting and feeling states under which they are administered. Without such appraisal the nature of the sensitivity reaction cannot be accurately defined. It is obvious that summation of the effects of various factors is often important, and for optimal therapeutic effectiveness those which are most important must be defined and dealt with.

CONCLUSIONS

The same adaptive or protective reactions may occur in man in response to many different stimuli. The physician aims to define that aspect of the situation which is most pertinent to the given individual and proceed accordingly.

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